

What is claimed is:

- 1 1. An isolated transcription factor involved in a hedgehog-mediated signaling
2 pathway, said transcription factor comprising at least one phosphorylation site, wherein
3 said transcription factor is dephosphorylated in response to said hedgehog mediated
4 signaling pathway, and said transcription factor binds to a hedgehog response element.
- 1 2. The transcription factor of claim 1, wherein said hedgehog response element
2 is a sonic hedgehog response element (ShhRE).
- 1 3. The transcription factor of claim 2, wherein said sonic hedgehog response
2 element comprises a nucleic acid sequence comprising 5'-
3 GTTCTACATAATGCGCCG-3' (SEQ ID NO:1).
- 1 4. A method for modulating expression of a target gene, said method
2 comprising modulating the phosphorylation of a transcription factor that interacts with
3 a hedgehog response element, wherein said hedgehog response element is operatively
4 associated with said target gene.
- 1 5. The method of claim 4, wherein said target gene is involved in a hedgehog
2 signaling pathway.
- 1 6. The method of claim 4, wherein said phosphorylation of said transcription
2 factor is modulated by affecting the activity of a phosphatase.
- 1 7. The method of claim 4, wherein said modulation is inhibition.
- 1 8. The method of claim 4, wherein said modulation is stimulation.

- 1 9. The method of claim 6, wherein said phosphatase is expressed from a
2 vector, said vector comprising a nucleic acid sequence which encodes said
3 phosphatase.
- 1 10. The method of claim 6, wherein said phosphatase is a PP2A phosphatase.
- 1 11. The method of claim 6, wherein said phosphatase is inhibited by a PP2A
2 phosphatase inhibitor.
- 1 12. The method of claim 11, wherein said phosphatase inhibitor is okadaic acid.
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- 1 13. The method of claim 11, wherein said phosphatase inhibitor is calyculin A.
- 1 14. The method of claim 4, wherein said hedgehog signaling pathway is
2 selected from the group consisting of Drosophila, Zebrafish, Xenopus, chicken, murine
3 and human hedgehog signaling pathways.
- 1 15. The method of claim 4, wherein said hedgehog signaling pathway is human
2 hedgehog signaling pathway.
- 1 16. The method of claim 4, wherein said transcription factor is a Ci/Gli
2 transcription factor family member.
- 1 17. The method of claim 16, wherein said transcription factor is Ci.
- 1 18. The method of claim 16, wherein said transcription factor is a Gli family
2 member.

- 1 19. The method of claim 4, wherein said response element is a Ci-response
2 element.
- 1 20. The method of claim 4, wherein said response element is a Gli-response
2 element.
- 1 21. The method of claim 4, wherein said response element is a sonic hedgehog
2 response element.
- 1 22. The method of claim 21, wherein said sonic hedgehog response element
2 comprises a nucleic acid sequence comprising 5'-GTTCTACATAATGCGCCG-3'
3 (SEQ ID NO:1).
- 1 23. The method of claim 21, wherein said transcription factor interacts with
2 said sonic hedgehog response element.
- 1 24. The method of claim 4, wherein said target gene is the ptc gene.
- 1 25. The method of claim 4, wherein said target gene is a gene encoding COUP-
2 TFII.
- 1 26. A method for modulating proliferation or differentiation of neuronal cells
2 comprising modulating the phosphorylation of a transcription factor that interacts with
3 a hedgehog response element operatively associated with a target gene, said target gene
4 encoding a polypeptide that modulates proliferation or differentiation of neuronal cells.
- 1 27. The method of claim 26, wherein said target gene encodes COUP-TFII.

1 28. The method of claim 26, further comprising detecting the proliferation or
2 differentiation of said neuronal cells.

1 29. The method of claim 28, wherein said detecting comprises assaying for the
2 presence of a neuronal marker.

1 30. The method of claim 29, wherein said neuronal marker is selected from the
2 group consisting of Isl1, HNF3 β and SC-1.

1 31. A method for treating a cell proliferative disorder in a subject, said method
2 comprising modulating the phosphorylation of a transcription factor that interacts with
3 a hedgehog response element by administering to the subject a modulating effective
4 amount of a phosphatase inhibitor.

1 32. The method of claim 31, wherein said response element is operatively
2 associated with a target gene.

1 33. The method of claim 32, wherein said target gene is the ptc gene.

1 34. The method of claim 31, wherein the cell proliferative disorder is selected
2 from the group consisting of basal cell carcinoma, medulloblastoma and meningioma.

1 35. A method for inhibiting bone defects in a subject, said method comprising
2 modulating the phosphorylation of a transcription factor that interacts with a hedgehog
3 response element operatively associated with a target gene, said target gene encoding a
4 polypeptide involved in mediating bone development.

1 36. A method for diagnosing a hedgehog signaling pathway-mediated familial
2 midline defect in a subject comprising determining the level of phosphorylated
3 transcription factor as compared to the level of dephosphorylated transcription factor,
4 wherein said transcription factor interacts with a hedgehog response element in
5 response to said hedgehog signaling pathway; and correlating said level of
6 phosphorylated transcription factor as compared to said level of dephosphorylated
7 transcription factor with the susceptibility for a familial midline defect.

1 37. The method of claim 36, wherein said familial midline defect is selected
2 from the group consisting of cyclopia and neural tube defect.

1 38. A method for identifying a compound that inhibits a phosphatase involved
2 in a hedgehog signaling pathway comprising:

3 a) incubating components comprising the compound, a
4 transcription factor that binds to a hedgehog response element operatively associated
5 with a target gene, and a phosphatase, under conditions sufficient to allow the
6 components to interact; and

7 b) measuring the ability of the compound to affect the hedgehog
8 signaling pathway by detecting an increase or decrease in expression of the target
9 gene.

1 39. The method of claim 38, wherein the hedgehog signaling pathway is the
2 sonic hedgehog signaling pathway.

1 40. The method of claim 38, wherein the target gene is chloramphenicol acetyl
2 transferase (CAT).

1 41. The method of claim 38, wherein the target gene is a lacZ gene.

1 42. The method of claim 38, wherein the response element is ShhRE.

1 43. The method of claim 38, wherein detection of expression is by detection of
2 protein product.

1 44. The method of claim 38, wherein detection of expression is by detection of
2 mRNA.

1 45. The method of claim 38, wherein the target gene further includes a reporter
2 means is selected from the group consisting of a radioisotope, a fluorescent compound,
3 a bioluminescent compound, a chemiluminescent compound, a metal chelator, or an
4 enzyme.

1 46. A method for identifying a compound which affects a hedgehog signaling
2 pathway comprising:

3 a) incubating components comprising the compound, a
4 phosphorylated transcription factor that binds to a hedgehog response element and a
5 phosphatase, under conditions sufficient to allow the components to interact; and

6 b) measuring the ability of the compound to affect hedgehog
7 signaling pathway by detecting the phosphorylation state of the transcription factor in
8 the presence and absence of the compound.